Properly Valuing Investment in the Development of Gene Replacement Therapy

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Many people are inclined to respond that high drug prices are their biggest concern with the market for healthcare in the United States. It is easy to see why they might feel this way: The news regularly trumpets new drugs coming on the market at eye-popping prices that few people could afford if they had to pay for it out of pocket.

The fact is, very few people find themselves subject to such prices, and health insurance or the government covers most of their costs.

As novel, transformative drugs and treatments begin to come to market, it is critical to understand the opportunity cost of foregoing such drugs compared to the high list prices these treatments may have. The value of breakthrough treatments on the broader health care system, including private and public payers, downstream healthcare use, and others should be considered along with the impact such drugs have on patients' out-of-pocket expenses and overall patient well-being when evaluating their potential coverage and utilization.

Some of the more expensive treatments hitting the market today are gene and cell therapies. Gene therapy aims to repair, replace, or simply deactivate "dysfunctional" genes in order to restore or establish normal functions. By attempting to address the underlying cause of a disease, rather than just treating the symptoms, gene therapies can often present a

cure for a fatal or debilitating disease, frequently with a one-time treatment. Compared to traditional pharmaceuticals that must be taken frequently over the course of a lifetime, gene therapies represent a truly transformative solution.

Some have suggested that an organ transplant may be a more helpful framework for understanding gene therapy: In-the-body gene therapies, which inject a therapeutic gene directly into the bloodstream, as well as out-of-the-body gene therapy, which involves extraction and separation of cells from blood or bone marrow, are both fundamentally different from traditional "small molecule" pharmaceutical treatments.[1] Each has been shown to dramatically and positively affect patients with certain rare and hard-to-treat diseases such as sickle cell disease, hemophilia, childhood acute lymphoblastic leukemia, spinal muscular atrophy, and others.

Foregoing a potential disease-curing therapy entails maintaining the existing treatment for a chronic illness or else a hastened death. Besides the patients' continued pain and suffering, the status quo protocol imposes a significant cost to the healthcare system--as well as the broader economy--on their own.

In the context of those costs, gene therapy and other novel therapies can be seen not only as cost-effective treatments that benefit the broader economy, but also as harbingers for potentially enormous improvements in human health and well-being.

[1] https://www.scientificamerican.com/article/experts-gene-therapy/

Properly Accounting for the Value of a Life Saved

To determine the value of any health or safety intervention we need to attach a dollar amount for each life that is saved, prolonged, or improved. It is, of course, a devilishly difficult and complicated task: while we might presume that someone whose life hangs in the balance would place a near-infinite value on that life, society cannot afford to do everything.

It is paramount to distinguish between the value of a statistical life and the amount we might devote to saving an individual or a family in perilous, life-threatening circumstance. The value of a statistical life is useful for public policy discussions where we do need to make trade-offs, because we cannot do everything. Spending $10 trillion on a program that will save one life is clearly not a wise use of scarce resources.

Another reason why public policy should not, as a rule, view life as infinitely valuable is that we do not behave in a way suggesting we view our own lives as infinitely valuable. There is a robust literature in the economics of risk that examines human behavior to determine how much we implicitly value our own lives, as reflected by everyday choices we make. For instance, occupations that involve cutting down trees or mining coal have a greater probability of injury or death than telemarketers. We can look at the broad difference in compensation between various professions with varying degrees of risk, control for other variables that impact compensation, and posit that at least a portion of the difference that remains reflects a wage premium necessary to induce people on the margin to work at a riskier job.

People make other choices that economists believe reveal the implicit value we place on our life. For instance, before anti-lock brakes became required on all new automobiles we could observe people's decisions about acquiring them. These sorts of considerations also apply to safer bicycle helmets, rear window cameras in automobiles, and various other safety features that can reduce the chance of injury or death from a crash. From

such choices, economists can estimate a rough value that people place on avoiding injury or death.

Finally, psychologists and other social scientists have studied and developed ways to express very low probabilities so that people can comprehend them and make speculative decisions about risk based on that information. For instance, even the most dangerous jobs in the U.S. have a low probability of accident or death. The timber industry employs approximately 100,000 loggers. In 2010, 70 loggers lost their lives, or .07 percent of the group. Most people have a difficult time conceptualizing that probability without being given some sort of context.

Several researchers have presented such probabilities to groups of people to ask them what sort of financial or other compensation they would need to accept a modest increase in what is already a very small risk of death.

Federal agencies that regulate consumer safety, transportation, the environment or the workplace need to incorporate some value of a life saved in cost-benefit analyses of proposed regulations, since the justification for most of them is a reduction in injury or death. Given that their incentive, from a public-choice perspective, would be to increase safety regulations and reduce deaths regardless of the attendant costs, we would expect that they will endeavor to use a higher value for a life saved.

And this tends to be what we observe. The Environmental Protection Agency (EPA), for instance, has effectively adopted a "Value of a Statistical Life," or VSL, of nearly $10 million, well beyond what could be justified based on the consensus literature. However, for a government regulator imposing a higher value for a life saved often does not constrain any government budget, so they do not recognize a direct trade off from a public-choice perspective.

But because Medicare and Medicaid play such a large role in the market, the government has a different perspective with regards to regulatory oversight in healthcare.

Health care does not typically use a VSL in its decision-making because it is not quite appropriate to assume that all lives are equal. For starters, many health interventions fail to cure illnesses, but do manage to extend lives; an intervention that postpones death by a couple months would be judged by most people as being worth less than one that buys a patient two more years.

It also makes sense to consider the quality of a life extended. For example, for people with kidney disease, there is a big difference between a life on dialysis--a thrice-weekly, physically debilitating procedure that makes work or travel difficult--or life after a kidney transplant that restores a great deal of their previous quality of life.

In medicine, we replace the Value of a Statistical Life with a metric called a Quality-Adjusted Life-Year, or QALY. The value is typically set administratively and not derived from any revealed preference, unlike the VSL, although the ingredients to the QALY may incorporate some aspects of revealed preference insights--such as how people value being in a specific, less than perfect health state. It primarily represents the perspective of the regulator.

More importantly, the QALY and the VSL differ regarding the government incentives involved in imposing a value for each. While the government tends to favor a high VSL, a higher value for a QALY can constrain government: while Medicaid and Medicare may be entitlements, which means that the government must spend whatever it promises to provide, policymakers are aware that its future healthcare obligations are woefully underfunded, so its incentive is to impose a lower QALY threshold.

This perspective can lead to a penny-wise but pound-foolish short-term approach, however. A low QALY value may reduce spending on gene therapy and similar breakthrough innovations, saving money in the short run, but these therapies often promise a complete cure to a disease. That means a patient will be able to work, earn money, pay taxes and eschew

the doctors' visits and medicine and care that his prior chronic illness would entail.

While these innovative cures may seem expensive in the short-run, the long-run benefits they engender can easily make them cost-effective if we properly approach the intervention from a long-run perspective, even though they may not appear to be so to a government preoccupied with short-term budget exigencies.

The True Opportunity Cost of Not Doing Gene Therapy

The cost of a course of treatment for a gene therapy regime alone actually overstates the incremental cost of the treatment to the health care provider. If it rejects the therapy then the patient must turn to the alternative treatment instead, if one even exists, and these treatments are not necessarily more affordable when we properly account for all costs involved.

For instance, the standard treatment for acute lymphoblastic leukemia costs an average of $40,000 for the first year alone. While the standard regime has come to be remarkably successful, with a five year survival rate at 68 percent, those afflicted with the disease who do survive must continue to receive treatment and follow up care for years. And those for whom the initial treatment fails will receive different treatments and invariably need to undergo future hospitalizations and all that entails.

A potential gene therapy treatment for hemophilia has a similar calculus. The average annual medical costs associated with treating someone with the disease, which involve the regular use of one of a number of different drugs, currently average $270,000. A one-time treatment for hemophilia that obviates the need for such regular pharmaceutical use would likely reduce overall health care expenditures for the illness even at a seven-figure price tag.

But even this comparison does not take into account substantial non-health care costs borne directly by the patients, who must endure the pain and hassle of multiple doctors visits, hospital readmissions, lost days at work, and general pain and suffering.

It is not just the patients that benefit from these advances: taxpayers stand to gain as well from potentially curative treatments. The government, through both Medicare and Medicaid, bears most of the cost of treating chronic illnesses via higher hospital admissions and other indirect treatment costs; employers and patients also bear a significant additional burden through missed work days or a premature end to employment altogether, resulting in a concomitant loss of income and, for governments, a second cost in the form of lost tax revenue. In other words, the government potentially stands to gain from the development of these therapies if they properly view them from a long-term budgetary perspective.

ICER and its Impact on Decision-making

The Institute for Clinical and Economic Review (ICER) is a nonprofit research institute founded nearly 15 years ago that does research on the clinical success and cost-effectiveness of medical treatments, tests, and procedures. Its stated goal is to help decision-makers understand and apply evidence to improve value throughout the health care system.

However, the public perception of ICER has gradually changed as its key offering, the ICER Value Assessment Framework, began to attract increased scrutiny. This shift accelerated in 2015, when ICER launched an endeavor aimed at evaluating new pharmaceuticals: the Emerging Therapy Assessment and Pricing (ETAP) program.

Over the course of its relatively short existence, ICER has become a formidable force in the health-care marketplace. Many insurers use the Value Assessment Framework to guide their decisions on which drugs and medical services to pay for, as well as how much to pay.

Estimating the value of a therapy or drug's efficacy is never a straightforward exercise. It requires placing some valuation not just on months or years of life saved, but also on an improved quality of life--or the value of an incremental improvement over an existing, less expensive drug.

Such measurements are fraught with complications. Promoting and over-relying on analyses conducted by an insurer-created entity may present a conflict of interest and lead insurers to forego covering treatments that patients need and that are cost-effective from a societal perspective. If an ICER report concludes that a drug, device, or treatment is overpriced, insurers can argue that they should not have to cover it or else pay much less than the company's posted price. Sharply lower drug prices may seem at first blush to be an unalloyed victory for consumers. But if manufacturers cannot recoup the costs of developing and testing drugs, then we will see less development of innovative cures.

These concerns extend to ICER's ETAP program, which was launched, according to ICER, to address "a major area of conflict in the U.S. healthcare system: rapidly rising costs for innovative new drugs." It released its first reports in late 2015, to some stiff criticism. For example, Peter Neumann and Joshua Cohen, writing in the New England Journal of Medicine, called into question the efficacy of ETAP's approach in its analysis of PCSK9 inhibitor drug prices, which it recommended reducing from over $14,000 to $2,177 per year. These drugs effectively treat individuals with high cholesterol, including high-risk patients who have not responded well to other treatments.

Following the ETAP report, prescriptions for these medicines were frequently rejected. The authors argued that ICER employed an overly rigid approach that goes well beyond mere cost-benefit analysis and injects arbitrary policy goals and metrics into decision-making.

Similar concerns have been raised with regard to ICER's approach toward evaluating new gene therapies, which treat, cure, or ultimately prevent disease by changing the expression of a person's genes. Around 4,000 diseases have been linked to genetic disorders, and gene therapies could potentially save or improve millions of lives.

In January 2018, ICER announced that Spark Therapeutic Inc.'s groundbreaking one-time gene therapy for a rare form of blindness was priced far too high. It has proactively evaluated the cost-effectiveness of Novartis's soon-to-be-approved spinal muscular atrophy gene therapy, Zolgensma, using a similar model, declaring an "appropriate" price of $2 million per treatment[2], as compared to currently available traditional drug treatments.

A common complaint is that ICER's evaluation system is overly rigid and imposes a "one size fits all" framework on complex drug-pricing decisions. A recent report by the policy-analysis group Xcenda noted that ICER's recommendations could significantly limit patient access to a wide variety of therapies for Medicare Part B beneficiaries. It seems likely that the same would be true for the broader population.

While ICER does not have authority over reimbursement decisions, the credibility afforded by its ostensibly independent status has led payers and pharmacy benefit managers to use ICER's analyses to establish coverage

[2] https://www.biopharmadive.com/news/gene-therapy-could-be-cost-effective-in-sma-but-not-at-4m/544969/

criteria, determine formulary placement, and negotiate discounts from drug manufacturers.

Rather than overlying on ICER assessments, policymakers should view these as just one additional data point. To maximize the full cost-savings benefits of gene and cell therapies, policymakers and payers alike must take into account a wider set of criteria, including societal costs that can be eliminated – for the first time – by disease cures.

The Path Forward

The eminent economist Mark Pauly has argued that individuals should be able to choose health plans with different QALY thresholds for coverage of treatment options. People with preferences for expansive coverage of all viable options, whatever the cost—say, $500,000 per QALY saved—would have all such services covered. And they would pay a higher premium for their health insurance. Conversely, people with preferences consistent with a $100,000 per QALY saved threshold would obtain coverage at a lower premium.

Ex post regret could become an issue with such an insurance policy, although this is in principle no different from someone who chooses to forgo collision coverage in automobile insurance only to wreck their car. Regret abounds in such a scenario. Nevertheless, coverage of costlier treatments could be available for the regretful consumer, perhaps with cost-sharing.

The clear role of public policy here is to ensure high quality studies to arrive at meaningful and understandable QALY values, and to make certain that consumers are able to understand the trade-offs involved between different coverage options.

The virtue of allowing consumer choice is that a one-size, top-down approach that uses a semi-transparent algorithm to decide what should be

covered and at what price does not fit everyone. The risk averse, those in poorer health, or individuals who simply value options may see things differently than enlightened and--indeed--well-intentioned bureaucrats.

The point is that transparent market signals will be sent to consumers in the form of health insurance premiums and those signals will induce enrollment behavior. It works now for deductible levels and other forms of cost-sharing: higher cost-sharing results in lower premiums, and consumers choose in accordance with their preferences. Importantly, a willingness to enroll in high QALY plans will serve as a pricing signal to innovative manufacturers. In other words, the explicit consequences of higher prices would be manifested in the form of fewer potential consumers.

In short, it is just what the healthcare sector needs: more market forces and less government coercion.

Properly Accounting for Health Care Gains

The list prices for today's cutting-edge gene therapy treatments invariably elicit outrage, which is usually the intent whenever they are referenced.

The customary response to this outcry has been to point out the very high costs of researching and developing such therapies, which can easily exceed $1 billion after testing for safety and efficacy. Without high margins, these drugs may never be created to begin with.

We suggest that we take care to consider the healthcare costs that would be incurred in the absence of such treatments, which have the potential to cure chronic or potentially deadly diseases. We submit that if we properly quantify the value of a life saved, as well as take into account the potential treatment costs throughout our healthcare system that would be necessary otherwise, many of these therapies should be properly viewed as

cost-effective interventions even without considering the substantial price discounts typically given to insurance companies and other providers.

Any honest discussion of the cost of gene therapy or other blockbuster discoveries should acknowledge this reality.